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 NEWS 10  JAN 07  WPIDS, WPINDEX, and WPIX enhanced Japanese Patent
                  Classification Data
 NEWS 11  FEB 02  Simultaneous left and right truncation (SLART) added
                  for CERAB, COMPUAB, ELCOM, and SOLIDSTATE
 NEWS 12  FEB 02  GENBANK enhanced with SET PLURALS and SET SPELLING
 NEWS 13  FEB 06  Patent sequence location (PSL) data added to USGENE
 NEWS 14  FEB 10  COMPENDEX reloaded and enhanced

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L1        4675 (INSULIN(W) RECEPTOR(W) SUBSTRATE(W) 2 OR IRS(W) 2)

=> s l1 and (over(w)express?)
L2          36 L1 AND (OVER(W) EXPRESS?)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3           22 DUP REM L2 (14 DUPLICATES REMOVED)

=> dis ibib abs l3 1-22

L3   ANSWER 1 OF 22  EMBASE  COPYRIGHT (c) 2009 Elsevier B.V. All rights
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ACCESSION NUMBER:   2008436533  EMBASE
TITLE:              Momordica charantia (bitter melon) reduces plasma
                    apolipoprotein B-100 and increases hepatic insulin receptor
                    substrate and phosphoinositide-3 kinase interactions.
AUTHOR:             Nerurkar, Pratibha V., Dr. (correspondence); Lee, Yun
                    Kyung; Motosue, Megan
CORPORATE SOURCE:   Laboratory of Metabolic Disorders and Alternative Medicine,
                    Department of Molecular Biosciences and Bioengineering,
                    University of Hawaii at Manoa, Honolulu, HI 96816, United
                    States. pratibha@hawaii.edu
AUTHOR:             Adeli, Khosrow
CORPORATE SOURCE:   Research Institute, The Hospital for Sick Children,
                    University of Toronto, Toronto, ON M5G 1X8, Canada.
AUTHOR:             Nerurkar, Vivek R.
CORPORATE SOURCE:   Department of Tropical Medicine, Medical Microbiology and
                    Pharmacology, Asia-Pacific Institute of Tropical Medicine
                    and Infectious Diseases, University of Hawaii at Manoa,
                    Honolulu, HI 96813, United States.
SOURCE:             British Journal of Nutrition, (2008) Vol. 100, No. 4, pp.
                    751-759.
                    Refs: 42
                    ISSN: 0007-1145  E-ISSN: 1475-2662  CODEN: BJNUAV
PUBLISHER:          Cambridge University Press, Shaftesbury Road, Cambridge,
                    CB2 2RU, United Kingdom.
PUBLISHER IDENT.:   S 0007-1145(08)93743-0
COUNTRY:            United Kingdom
DOCUMENT TYPE:      Journal; Article
FILE SEGMENT:       003     Endocrinology
                    018     Cardiovascular Diseases and Cardiovascular Surgery
                    029     Clinical and Experimental Biochemistry
                    030     Clinical and Experimental Pharmacology
                    037     Drug Literature Index
LANGUAGE:           English
SUMMARY LANGUAGE:   English
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ENTRY DATE: Entered STN: 30 Sep 2008
Last Updated on STN: 30 Sep 2008

AB Aqueous extracts or juice from unripened fruit of Momordica charantia (bitter melon) has traditionally been used in the treatment of diabetes and its complications. Insulin resistance is characterized by significant down-regulation of hepatic insulin signalling as documented by attenuated phosphorylation of insulin receptor (IR), IR substrates 1 and 2, phosphoinositide-3 kinase, protein kinase B, and over-expression of phosphotyrosine phosphatase 1B. We recently demonstrated that bitter melon juice (BMJ) is a potent inhibitor of apoB secretion and TAG synthesis and secretion in human hepatoma cells, HepG2, that may be involved in plasma lipid- and VLDL-lowering effects observed in animal studies. The aim of this study was to evaluate the effects of BMJ on plasma apoB levels and hepatic insulin signalling cascade in mice fed high-fat diet (HFD). Female C57BL/6 mice (4-6 weeks old) were randomized into three groups receiving regular rodent chow, HFD and HFD+BMJ. The data indicate that BMJ not only improves glucose and insulin tolerance but also lowers plasma apoB-100 and apoB-48 in HFD-fed mice as well as modulates the phosphorylation status of IR and its downstream signalling molecules. Investigating the biochemical and molecular mechanisms involved in amelioration of diabetic dyslipidaemia by BMJ may lead to identification of new molecular targets for dietary/alternative therapies. .COPYRGT. The Authors 2008.

L3 ANSWER 2 OF 22 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2008174922 MEDLINE
DOCUMENT NUMBER: PubMed ID: 18221412
TITLE: Advances in vertebrate aging research 2007.
AUTHOR: Austad Steven
CORPORATE SOURCE: University of Texas Health Science Center, Barshop Center for Longevity and Aging Studies, San Antonio, TX 78245, USA.. austad@uthscsa.edu
SOURCE: Aging cell, (2008 Mar) Vol. 7, No. 2, pp. 119-24.
Electronic Publication: 2008-01-21.
Journal code: 101130839. E-ISSN: 1474-9726.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200803
ENTRY DATE: Entered STN: 13 Mar 2008
Last Updated on STN: 29 Mar 2008
Entered Medline: 28 Mar 2008

AB Among this year's highlights in vertebrate aging research, we find a study in which, contrary to the oxidative stress hypothesis of aging, reduced expression of a major cellular antioxidant, glutathione peroxidase 4, led to a small increase in mouse lifespan. By contrast, a large comparative proteomic analysis discovered a remarkably robust and previous unsuspected inverse association between species lifespan and relative frequency of cysteine residues in mitochondrially encoded respiratory chain proteins only, which the authors attribute to cysteine's ease of oxidation. Another study evaluated more cleanly than any previous work the hypothesis that blood glucose concentration is a key mediator of aging, and concluded that it wasn't. Several new mouse longevity mutants were also reported this year, some (PAPP-A, IRS-1, and IRS-2 knockouts) supporting previous work on the importance of insulin/insulin-like growth factor-1 signaling and aging. However, there were inconsistencies between laboratories in some of the results, which merit further investigation. Also, somewhat inconsistent with these findings, over-expression of insulin-like growth factor-1 in heart only lengthened life. From a completely new direction, type 5 adenylyl cyclase knockout mice were observed to live more than 30% longer than controls.

Finally, a new program for evaluating potential pharmaceutical interventions in aging and longevity made its appearance, and is notable at this point chiefly for the excellence of its experimental design. A similar program for the disinterested evaluation of reported longevity mutations in mice would be a service to the community of vertebrate aging researchers.

L3 ANSWER 3 OF 22 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2008349612 EMBASE
TITLE: Important genetic checkpoints for insulin resistance in salt-sensitive (S) Dahl rats.
AUTHOR: Shehata, Marlene F. (correspondence)
CORPORATE SOURCE: Department of Cellular and Molecular Medicine, University of Ottawa Heart Institute, Ottawa, ON K1Y 4W7, Canada. mshehata@ottawaheart.ca
SOURCE: Cardiovascular Diabetology, (21 Jun 2008) Vol. 7. arn. 19. Refs: 133
E-ISSN: 1475-2840 CODEN: CDAIAZ
PUBLISHER: BioMed Central Ltd., 34 - 42 Cleveland Street, London, W1T 4LB, United Kingdom.
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
022 Human Genetics
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Aug 2008
Last Updated on STN: 1 Aug 2008

AB Despite the marked advances in research on insulin resistance (IR) in humans and animal models of insulin resistance, the mechanisms underlying high salt-induced insulin resistance remain unclear. Insulin resistance is a multifactorial disease with both genetic and environmental factors (such as high salt) involved in its pathogenesis. High salt triggers insulin resistance in genetically susceptible patients and animal models of insulin resistance. One of the mechanisms by which high salt might precipitate insulin resistance is through its ability to enhance an oxidative stress-induced inflammatory response that disrupts the insulin signaling pathway. The aim of this hypothesis is to discuss two complementary approaches to find out how high salt might interact with genetic defects along the insulin signaling and inflammatory pathways to predispose to insulin resistance in a genetically susceptible model of insulin resistance. The first approach will consist of examining variations in genes involved in the insulin signaling pathway in the Dahl S rat (an animal model of insulin resistance and salt-sensitivity) and the Dahl R rat (an animal model of insulin sensitivity and salt-resistance), and the putative cellular mechanisms responsible for the development of insulin resistance. The second approach will consist of studying the over-expressed genes along the inflammatory pathway
whose respective activation might be predictive of high salt-induced insulin resistance in Dahl S rats. Variations in genes encoding the insulin receptor substrates -1 and/or -2 (IRS-1, -2) and/or genes encoding the glucose transporter (GLUTs) proteins have been found in patients with insulin resistance. To better understand the combined contribution of excessive salt and genetic defects to the etiology of the disease, it is essential to investigate the following question: Question 1: Do variations in genes encoding the IRS -1 and -2 and/or genes encoding the GLUTs proteins predict high salt-induced insulin resistance in Dahl S rats? A significant amount of evidence suggested that salt-induced oxidative stress might predict an inflammatory response that upregulates mediators

of inflammation such as the nuclear factor- kappa B (NF-kappa B), the tumor necrosis factor-alpha (TNF-α) and the c-Jun Terminal Kinase (JNK). These inflammatory mediators disrupt the insulin signaling pathway and predispose to insulin resistance. Therefore, the following question will be thoroughly investigated: Question 2: Do variations in genes encoding the NF-kappa B, the TNF-α and the JNK, independently or in synergy, predict an enhanced inflammatory response and subsequent insulin resistance in Dahl S rats in excessive salt environment? Finally, to better understand the combined role of these variations on glucose metabolism, the following question will be addressed: Question 3: What are the functional consequences of gene variations on the rate of glucose delivery, the rate of glucose transport and the rate of glucose phosphorylation in Dahl S rats? The general hypothesis is that "high-salt diet in combination with defects in candidate genes along the insulin signaling and inflammatory pathways predicts susceptibility to high salt-induced insulin resistance in Dahl S rats".

L3 ANSWER 4 OF 22 BIOSIS
ACCESSION NUMBER: 2007:602995 BIOSIS
DOCUMENT NUMBER: PREV200700606305
TITLE: Evaluation of fatty acid metabolism-related gene expression in nonalcoholic fatty liver disease.
AUTHOR(S): Nakamura, Makoto; Kohjima, Motoyuki; Nishi, Hidehiro; Enjoji, Munechika
SOURCE: Gastroenterology, (APR 2007) Vol. 132, No. 4, Suppl. 2, pp. A816.
Meeting Info.: Digestive Disease Week Meeting/108th Annual Meeting of the American-Gastroenterological-Association. Washington, DC, USA. May 19 -24, 2007. Amer Gastroenterol Assoc; Amer Assoc Study Liver Dis; Amer Soc Gastrointestinal Endoscopy; Soc Surg Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Dec 2007
Last Updated on STN: 6 Dec 2007

AB Background/Aims: Nonalcoholic fatty liver disease (NAFLD) is one of the most frequent causes of abnormal liver dysfunction, and its prevalence has markedly increased; however, the mechanisms involved in the pathogenesis of NAFLD have not been thoroughly investigated in humans. To clarify precise mechanisms of NAFLD, we evaluated the expression of fatty acid metabolism-related genes. Methods: Real-time RT-PCR was performed using liver biopsy samples from 24 NAFLD patients and 10 normal controls. Results: In NAFLD, expression of acetyl-CoA carboxylase and fatty acid synthase involved in de novo fatty acid synthesis were increased. Adipose differentiation-related protein, which is related to up-take of fatty acids, was also increased. With regard to fatty acid oxidation, in mitochondria, long-chain acyl-CoA dehydrogenase and long-chain L-3-hydroxyacyl-coenzyme A dehydrogenase were up-regulated accompanying with the increased expression of uncoupling protein 2, whereas carnitine palmitoyltransferase la, a rate-limiting enzyme of mitochondrial oxidation, was down-regulated. In peroxisome, both straight-chain acyl-CoA oxidase and branched-chain acyl-CoA oxidase were up-regulated although PPAR alpha was down-regulated. In microsome, CYP2E1 and CYP4A11 were both over-expressed. SOD and catalase involved in antioxidant pathways were also over-expressed. In regard to lipid droplet formation, the expression of diacylglycerol O-acyltransferase 1 and PPAR gamma was increase whereas that of hormone sensitive lipase was decreased. Sterol regulatory element-binding protein Ic (SREBP1c), a transcriptional factor, positively regulates fatty acid

synthesis. SREBP1c is also negatively regulated by AMP-activated protein kinase (AMPK) and positively regulated by insulin. In NAFLD, SREBP1c expression was enhanced, and AMPK was decreased. Insulin receptor substrate (IRS) 2 was also decreased whereas IRS1 was unchanged. Conclusion: These data indicate as follows; increased de novo synthesis and up-take of fatty acid lead to further accumulation of them in hepatocytes, mitochondrial fatty acid oxidation is decreased or fully activated, and peroxisomal and microsomal oxidation was complementally up-regulated to decrease fatty acid accumulation, antioxidant pathways including SOD and catalase were enhanced to neutralize over-produced ROS by oxidation; lipid droplet formation was enhanced. The increased fatty acids synthesis, that is consider as a primary event in NAFLD, is attributable to enhanced SREBP1c which is under the control of balance between AMPK and insulin.

L3 ANSWER 5 OF 22 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2007384086 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17443674
TITLE: Dual regulation of upstream binding factor 1 levels by IRS-1 and ERKs in IGF-1-receptor signaling.
AUTHOR: Sun Hongzhi; Tu Xiao; Liu Mingli; Baserga Renato
CORPORATE SOURCE: Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA 19107, USA.
CONTRACT NUMBER: 089640
SOURCE: Journal of cellular physiology, (2007 Sep) Vol. 212, No. 3, pp. 780-6.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200709
ENTRY DATE: Entered STN: 3 Jul 2007
Last Updated on STN: 28 Sep 2007
Entered Medline: 27 Sep 2007
AB The Upstream Binding Factor 1 (UBF1) is a nucleolar protein that participates in the regulation of RNA polymerase I activity and ribosomal RNA (rRNA) synthesis. In 32D myeloid cells expressing the type 1 insulin-like growth factor receptor (IGF-IR), the UBF1 protein (but not its mRNA) is down regulated when the cells are shifted from Interleukin-3 (IL-3) to IGF-1. Ectopic expression of insulin receptor substrate-1 (IRS-1) in these cells inhibits the down-regulation of UBF1. We now show that the stability of UBF1 in 32D-derived cells requires also a signal from the extracellular regulated kinases (ERKs). When ERKs signaling is defective, as in cells over-expressing the insulin receptor (InR) or selected mutants of the IGF-1R, UBF1 is down-regulated, even in the presence of IRS-1. The down-regulation is corrected by the expression of an activated Ha-ras, which stimulates ERKs activity. Mutations at threonines 117 and 201 of UBF1, known to be phosphorylated by ERKs, cause its down-regulation. However, when IRS-2, instead of IRS-1, is ectopically expressed in 32D InR cells, ERKs phosphorylation is increased and UBF is stabilized. Taken together, these results indicate that in 32D-derived myeloid cells expressing either the IGF-IR or the InR, UBF1 levels are regulated by signaling from both IRS proteins and ERKs.

L3 ANSWER 6 OF 22 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2007:602628 BIOSIS
DOCUMENT NUMBER: PREV200700605938
TITLE: Evaluation of fatty acid metabolism-related gene expression in nonalcoholic fatty liver disease.

AUTHOR(S): Nakamuta, Makoto; Kohjima, Motoyuki; Nishi, Hidehiro; Enjoji, Munechika
SOURCE: Gastroenterology, (APR 2007) Vol. 132, No. 4, Suppl. 2, pp. A737.
Meeting Info.: Digestive Disease Week Meeting/108th Annual Meeting of the American-Gastroenterological-Association. Washington, DC, USA. May 19 -24, 2007. Amer Gastroenterol Assoc; Amer Assoc Study Liver Dis; Amer Soc Gastrointestinal Endoscopy; Soc Surg Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Dec 2007
Last Updated on STN: 6 Dec 2007

AB Background/Aims: Nonalcoholic fatty liver disease (NAFLD) is one of the most frequent causes of abnormal liver dysfunction, and its prevalence has markedly increased; however, the mechanisms involved in the pathogenesis of NAFLD have not been thoroughly investigated in humans. To clarify precise mechanisms of NAFLD, we evaluated the expression of fatty acid metabolism-related genes. Methods: Real-time RT-PCR was performed using liver biopsy samples from 24 NAFLD patients and 10 normal controls. Results: In NAFLD, expression of acetyl-CoA carboxylase and fatty acid synthase involved in de novo fatty acid synthesis were increased. Adipose differentiation-related protein, which is related to up-take of fatty acids, was also increased. With regard to fatty acid oxidation, in mitochondria, long-chain acyl-CoA clehydrogenase and long-chain L-3-hydroKyacyl-coenzyme A clehydrogenase were up-regulated accompanying with the increased expression of uncoupling protein 2, whereas carnitine palmitoyltransferase la, a rate-limiting enzyme of mitochondrial oxidation, was down-regulated. in peroxisome, both straight-chain acyl-CoA oxiclase and branched-chain acyl-CoA oxidase were up-regulated although PPAR alpha was down-regulated. in microsome, CYP2E1 and CYP4A11 were both over-expressed, SOD and catalase involved in antioxidant pathways were also over-expressed. In regard to lipid droplet formation, the expression of diacylglycerol C-acyltransferase 1 and PPAR gamma was increase whereas that of hormone sensitive lipase was decreased. Sterol regulatory element-binding protein Ic (SREBP1c), a transcriptional factor, positively regulates fatty acid synthesis. SREBP1c is also negatively regulated by AMP-activated protein kinase (AMPK) and positively regulated by insulin. In NAFLD, SREBP1c expression was enhanced, and AMPK was decreased. Insulin receptor substrate (IRS) 2 was also decreased whereas IRS1 was unchanged.
Conclusion: These data indicate as follows; increased de novo synthesis and up-take of fatty acid lead to further accumulation of them in hepatocytes; mitochondrial fatty acid oxidation is decreased or fully activated, and peroxisomal and microsomal oxidation was complementally up-regulated to decrease fatty acid accumulation; antioxidant pathways including SOD and catalase were enhanced to neutralize over-produced ROS by oxidation; lipid droplet formation was enhanced. The increased fatty acids synthesis, that is consider as a primary event in NAFLD, is attributable to enhanced SREBP1c which is under the control of balance between AMPK and insulin.

L3 ANSWER 7 OF 22 EMBASE DUPLICATE 3
ACCESSION NUMBER: 2007553895 EMBASE
TITLE: Preeclampsia, insulin signalling and immunological dysfunction: a fetal, maternal or placental disorder?.
AUTHOR: Rademacher, Thomas W.
CORPORATE SOURCE: Department of Immunology and Molecular Pathology, Molecular Medicine Unit, Royal Free and University College London

Medical School, London, United Kingdom.
AUTHOR: Gumaa, Khalid
CORPORATE SOURCE: College of Medicine and Medical Sciences, Arabian Gulf University, Manama, Bahrain.
AUTHOR: Scioscia, Marco (correspondence)
CORPORATE SOURCE: Department of Gynaecology, Obstetrics and Neonatology, University of Medical Science of Bari, Policlinico of Bari, Piazza Giulio Cesare 11, 70125 Bari, Italy. marcoscioscia@gmail.com
SOURCE: Journal of Reproductive Immunology, (Dec 2007) Vol. 76, No. 1-2, pp. 78-84.
Refs: 51
ISSN: 0165-0378 CODEN: JRIMDR
PUBLISHER IDENT.: S 0165-0378(07)00090-3
COUNTRY: Ireland
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 010 Obstetrics and Gynecology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Dec 2007
Last Updated on STN: 21 Dec 2007

AB An inappropriate glycogen accumulation in preeclamptic placentas was described as secondary to biochemical alterations. Insulin resistance is widely accepted to be associated with preeclampsia, although its basis remain unclear. A family of putative insulin mediators, namely inositol phosphoglycans, were described to exert many insulin-like effects on lipid and glucose metabolism. A definite association between the P-type mediator (P-IPG) and preeclampsia was reported, being increased in placenta, urine, amniotic fluid and cord blood from human preeclamptic pregnancies. A strong link exists between insulin resistance and inflammation. Clear features of insulin resistance and systemic inflammatory activation were described in preeclampsia. It may be a consequence of the immunological dysfunction that occurs in preeclampsia that is temporized during sperm exposure and co-habitation which confuses the maternal immune network to perceive 'danger'. The over-expression of P-IPG during preeclampsia may be a counter-regulatory mechanism to insulin resistance since these molecules mimic insulin action. Besides, the lipidic form of P-IPG was reported to be similar to endotoxins, and may represent the 'danger signa'. We propose here a novel working theory on insulin resistance and preeclampsia.

L3 ANSWER 8 OF 22 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2006459225 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16871543
TITLE: Aspartyl-asparagyl beta hydroxylase over-expression in human hepatoma is linked to activation of insulin-like growth factor and notch signaling mechanisms.
AUTHOR: Cantarini M Chiara; de la Monte Suzanne M; Pang Maoyin; Tong Ming; D'Errico Antonia; Trevisani Franco; Wands Jack R
CORPORATE SOURCE: Department of Medicine, Rhode Island Hospital, Brown Medical School, Providence, RI 02903, USA.
CONTRACT NUMBER: AA-02169 (United States NIAAA)
AA-11431 (United States NIAAA)
AA02666 (United States NIAAA)
AA12908 (United States NIAAA)
CA-35711 (United States NCI)
P20RR15578 (United States NCRR)
SOURCE: Hepatology (Baltimore, Md.), (2006 Aug) Vol. 44, No. 2, pp. 446-57.

Journal code: 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
(IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 3 Aug 2006
Last Updated on STN: 25 Aug 2006
Entered Medline: 24 Aug 2006

AB Aspartyl-(asparagyl)-beta-hydroxylase (AAH) is overexpressed in various malignant neoplasms, including hepatocellular carcinomas (HCCs). The upstream regulation of AAH and its functional role in Notch-mediated signaling and motility in HCC cells was accessed. The mRNA transcript levels of AAH, insulin receptor substrate (IRS), insulin and insulin-like growth factor (IGF) receptors and polypeptides, Notch, Jagged, and HES were measured in 15 paired samples of HCC and adjacent HCC-free human liver biopsy specimens using real-time quantitative RT-PCR and Western blot analysis. Overexpression of AAH was detected in 87% of the HCC relative to the paired HCC-free liver tissue. IRS-1, IRS-2, and IRS-4 were each overexpressed in 80% of the HCC samples, and IGF-I and IGF-2 receptors were overexpressed in 40% and 100% of the HCCs, respectively. All HCC samples had relatively increased levels of Notch-1 and HES-1 gene expression. Overexpression of AAH led to increased levels of Notch, and co-immunoprecipitation experiments demonstrated a direct interaction between AAH and Notch as well as its ligand Jagged. In conclusion, contributions to the malignant phenotype of HCC is due to activation of IGF-I and IGF-II signaling that results in over-expression of both AAH and Notch. The functional role of AAH in relation to cell motility has been linked to increased activation of the Notch signaling pathway.

L3 ANSWER 9 OF 22 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2006282690 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16697063
TITLE: Trk receptor binding and neurotrophin/fibroblast growth factor (FGF)-dependent activation of the FGF receptor substrate (FRS)-3.
AUTHOR: Dixon Scott J; MacDonald James I S; Robinson Kim N; Kubu Christopher J; Meakin Susan O
CORPORATE SOURCE: Laboratory of Neural Signaling, Cell Biology Group, The John P. Robarts Research Institute, London, Ontario, Canada N6A 5K8.
SOURCE: Biochimica et biophysica acta, (2006 Apr) Vol. 1763, No. 4, pp. 366-80. Electronic Publication: 2006-03-21.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200607
ENTRY DATE: Entered STN: 23 May 2006
Last Updated on STN: 18 Jul 2006
Entered Medline: 17 Jul 2006

AB We have investigated the signaling properties of the fibroblast growth factor (FGF) receptor substrate 3 (FRS3), also known as SNT-2 or FRS2beta, in neurotrophin-dependent differentiation in comparison with the related adapter FRS2 (SNT1 or FRS2alpha). We demonstrate that FRS3 binds all neurotrophin Trk receptor tyrosine kinases and becomes tyrosine

phosphorylated in response to NGF, BDNF, NT-3 and FGF stimulation in transfected cells and/or primary cortical neurons. Second, the signaling molecules Grb2 and Shp2 bind FRS3 at consensus sites that are highly conserved among FRS family members and that Shp2, in turn, becomes tyrosine phosphorylated. While FRS3 over-expression in PC12 cells neither increases NGF-induced neuritogenesis nor activation of Map kinase/AKT, comparable to previous reports on FRS2, over-expression of a chimeric adapter containing the PH/PTB domains of the insulin receptor substrate (IRS) 2, in place of the PTB domain of FRS3 (IRS2-FRS3) supports insulin-dependent Map kinase activation and neurite outgrowth in PC12 cells. Collectively, these data demonstrate that FRS3 supports ligand-induced Map kinase activation and that the chimeric IRS2-FRS3 adapter is stimulating sufficient levels of activated MapK to support neurite outgrowth in PC12 cells.

L3 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1262633 CAPLUS
DOCUMENT NUMBER: 144:17598
TITLE: Receptor binding specificity of herstatin and its use in the treatment of refractory cancers
INVENTOR(S): Clinton, Gail; Shamieh, Lara
PATENT ASSIGNEE(S): Oregon Health and Science University, USA
SOURCE: PCT Int. Appl., 167 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005112969	A2	20051201	WO 2005-US14029	20050422
WO 2005112969	A3	20060420		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2564538	A1	20051201	CA 2005-2564538	20050422
US 20050272637	A1	20051208	US 2005-113202	20050422
EP 1796711	A2	20070620	EP 2005-779957	20050422
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.:
US 2004-564893P P 20040422
US 2004-590473P P 20040723
WO 2005-US14029 W 20050422

AB The binding interactions between herstatin, or the intron 8-encoded receptor binding domain (RBD Int8) of the protein, and several receptors were analyzed. Herstatin and the intron 8-encoded domain bind with high affinity (e.g., nanomolar concns.) to all four of the ErbB receptors: EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); and HER-4 (erbB-4), as well as to ?EGFR and the IGF-1 receptor, and such binding has utility to modulate signaling mediated by these receptors. Herstatin inhibited target receptor-mediated activation of intracellular signaling pathways (e.g., PI3/Akt, IRS-2, etc., pathways) that

are important in cell survival, and further inhibited target receptor-mediated (e.g., IGF-1/IGF-1R-mediated) survival of cancer cells. Aspects of the present invention thus provide methods and compns. for the treatment of cancer, including cancer refractory to other erbB-based agents, and of other conditions and disorders characterized by target receptor expression, over-expression, signaling, and/or aberrant signaling. Addnl. aspects provide methods of targeted drug delivery.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 22 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:247465 BIOSIS
DOCUMENT NUMBER: PREV200510038239
TITLE: Hepatocyte CYP2E1 overexpression and steatohepatitis lead to impaired hepatic insulin signaling.
AUTHOR(S): Schattenberg, Jorn M.; Wang, Yongjun; Singh, Rajat; Rigoli, Raina M.; Czaja, Mark J. [Reprint Author]
CORPORATE SOURCE: Albert Einstein Coll Med, Marion Bessin Liver Res Ctr, 1300 Morris Pk Ave, Bronx, NY 10461 USA
czaja@aecom.yu.edu
SOURCE: Journal of Biological Chemistry, (MAR 18 2005) Vol. 280, No. 11, pp. 9887-9894.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Jul 2005
Last Updated on STN: 8 Jul 2005

AB Insulin resistance and increased cytochrome P450 2E1 (CYP2E1) expression are both associated with and mechanistically implicated in the development of nonalcoholic fatty liver disease. Although currently viewed as distinct factors, insulin resistance and CYP2E1 expression may be interrelated through the ability of CYP2E1-induced oxidant stress to impair hepatic insulin signaling. To test this possibility, the effects of in vitro and in vivo CYP2E1 overexpression on hepatocyte insulin signaling were examined. CYP2E1 overexpression in a hepatocyte cell line decreased tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2 in response to insulin. CYP2E1 overexpression was also associated with increased inhibitory serine 307 and 636/639 IRS-1 phosphorylation. In parallel, the effects of insulin on Akt activation, glycogen synthase kinase 3, and FoxO1a phosphorylation, and glucose secretion were all significantly decreased in CYP2E1 over-expressing cells. This inhibition of insulin signaling by CYP2E1 overexpression was partially c-Jun N-terminal kinase dependent. In the methionine- and choline-deficient diet mouse model of steatohepatitis with CYP2E1 overexpression, insulin-induced IRS-1, IRS-2, and Akt phosphorylation were similarly decreased. These findings indicate that increased hepatocyte CYP2E1 expression and the presence of steatohepatitis result in the down-regulation of insulin signaling, potentially contributing to the insulin resistance associated with nonalcoholic fatty liver disease.

L3 ANSWER 12 OF 22 EMBASE COPYRIGHT (c) 2009 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005199769 EMBASE
TITLE: The GLUTs family - Lessons from transgenic mice.
AUTHOR: Hartil, K.; Weldon, R.H.; Seki, Y.; Charron, M.J. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, United States. charron@aecom.yu.edu

SOURCE: Current Medicinal Chemistry: Immunology, Endocrine and Metabolic Agents, (Apr 2005) Vol. 5, No. 2, pp. 189-206. Refs: 144
ISSN: 1568-0134 CODEN: CMCIC8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
029 Clinical and Experimental Biochemistry
003 Endocrinology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 May 2005
Last Updated on STN: 19 May 2005

AB The glucose transporters (GLUTs) are currently a 13 member family of facilitative transmembrane proteins which transport glucose down its concentration gradient. The GLUTs have a tissue specific expression and regulation. Dysregulation of GLUTs have been implicated in the pathogenesis of a number of diseases including diabetes and cancer and are known to play an important role in the developing embryo. In addition, roles for GLUTs in cardiac function and embryonic development have been identified and will be discussed in this review. The ability to ablate or over-express GLUTs has advanced our understanding of the role these transporters play in the maintenance of normal glucose homeostasis and the pathogenesis of diabetes. The development of Cre-LoxP technology coupled with the existence of tissue specific promoters allows investigators to manipulate gene expression both globally and in a tissue specific manner. The major GLUTs which have been investigated using transgenic technology are GLUT1, GLUT4 and GLUT2. Overexpression of GLUT4 and GLUT1 results in increased glucose uptake and metabolism. However, only GLUT4 overexpression protects against the development of insulin resistance in transgenic mice. Genetic ablation of GLUT4 and GLUT2 results in impaired insulin tolerance and defects in both lipid and glucose metabolism. This review will present various transgenic models of GLUT modification and discuss what has been learned from these models about the role that GLUTs play in glucose homeostasis, insulin action and development. .COPYRGT. 2005 Bentham Science Publishers Ltd.

L3 ANSWER 13 OF 22 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:299708 BIOSIS
DOCUMENT NUMBER: PREV200510093733
TITLE: Regulation of IGF-I signalling in cardiomyocytes in adhesion.
AUTHOR(S): O'Donovan, H. C. [Reprint Author]; O'Connor, R.
CORPORATE SOURCE: BioSci Inst, Cork, Ireland
SOURCE: Molecular Biology of the Cell, (NOV 2004) Vol. 15, No. Suppl. S, pp. 14A.
Meeting Info.: 44th Annual Meeting of the American-Society-for-Cell-Biology. Washington, DC, USA. December 04 -08, 2004. Amer Soc Cell Biol.
CODEN: MBCEEV. ISSN: 1059-1524.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Aug 2005
Last Updated on STN: 15 Aug 2005

L3 ANSWER 14 OF 22 EMBASE DUPLICATE 6

ACCESSION NUMBER: 2003239564 EMBASE
TITLE: Retinoic acid-induced growth arrest of MCF-7 cells involves the selective regulation of the IRS-1/PI 3-kinase/AKT pathway.
AUTHOR: Del Rincon, Sonia V.; Rousseau, Caroline; Samanta, Ratna; Miller Jr., Wilson H. (correspondence)
CORPORATE SOURCE: Lady Davis Inst. for Med. Research, Sir Mortimer B. Davis Jewish Gen. H., Departments of Oncology and Medicine, Montreal, Que., Canada. wmiller@ldi.jgh.mcgill.ca
AUTHOR: Miller Jr., Wilson H. (correspondence)
CORPORATE SOURCE: Lady Davis Institute, 3755 Cote Ste-Catherine Rd., Montreal, Que. H3T 1E2, Canada. wmiller@ldi.jgh.mcgill.ca
SOURCE: Oncogene, (29 May 2003) Vol. 22, No. 22, pp. 3353-3360. Refs: 74
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 2003
Last Updated on STN: 3 Jul 2003

AB In the MCF-7 breast cancer cell line, insulin-like growth factors (IGFs) are known to elicit antiproliferative actions via the insulin receptor substrate-1 (IRS-1)/PI 3-kinase/AKT pathway. All-trans retinoic acid (RA) is a potent inhibitor of MCF-7 cell proliferation, but the mechanism by which growth regulation is achieved remains unclear. We investigated the effects of RA on the regulation of the IGF-IR and its key signaling elements: IRS-1, IRS-2, and SHC. Treatment of MCF-7 cells with RA caused a significant reduction in IRS-1 protein and tyrosine phosphorylation levels at a concentration and time consistent with RA-mediated growth inhibition. IRS-1 regulation is selective, as RA did not influence IRS-2 or SHC levels. Downstream signaling events were also selectively reduced, as RA abrogated IGF-I-stimulated AKT activation but did not alter erk1/2 activation. To confirm the importance of IRS-1 regulation by RA, we examined the response to RA in MCF-7 cells over-expressing IGF-IR and IRS-1. RA resistance was observed in MCF-7 cells overexpressing IRS-1 but not IGF-IR. This suggests that RA-mediated growth inhibition requires the selective downregulation of IRS-1 and AKT. Therapeutic agents targeting the IRS-1/PI 3-kinase/AKT pathway may enhance the cytostatic effects of RA in breast cancer, since overexpression of IRS-1 and AKT have been reported in primary breast tumors.

L3 ANSWER 15 OF 22 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:131927 BIOSIS
DOCUMENT NUMBER: PREV200400134137
TITLE: Genetic alterations and aberrant expression of genes related to the phosphatidyl-inositol-3'-kinase/protein kinase B (Akt) signal transduction pathway in glioblastomas.
AUTHOR(S): Knobbe, Christiane B.; Reifenberger, Guido [Reprint Author]
CORPORATE SOURCE: Department of Neuropathology, Heinrich-Heine-University, Moorenstrasse 5, D-40225, Duesseldorf, Germany reifenberger@med.uni-duesseldorf.de
SOURCE: Brain Pathology, (October 2003) Vol. 13, No. 4, pp. 507-518. print.
ISSN: 1015-6305 (ISSN print).
DOCUMENT TYPE: Article

LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2004
Last Updated on STN: 10 Mar 2004

AB Glioblastomas frequently carry mutations in the PTEN tumor suppressor gene on 10q23.3. The tumor suppressor properties of Pten are closely related to its inhibitory effect on the phosphatidylinositol-3'-kinase (Pi3k)-dependent activation of protein kinase B (Akt) signalling. Here, we report on the analysis of 17 genes related to the Pi3kIAkt signalling pathway for genetic alteration and aberrant expression in a series of 103 glioblastomas. Mutation, homozygous deletion or loss of expression of PTEN was detected in 32% of the tumors. In contrast, we did not find any aberrations in the inositol polyphosphate phosphatase like-1 gene (INPPL1), whose gene product may also counteract Pi3k-dependent Akt activation. Analysis of genes encoding proteins that may activate the pathway upstream of Pi3k revealed variable fractions of tumors with EGFR amplification (31%), PDGFRA amplification (8%), and IRS2 amplification (2%). The protein tyrosine kinase 2 (PTK2/FAK1) gene was neither amplified nor over-expressed at the mRNA level.
Investigation of three genes encoding catalytic subunits of Pi3k (PIK3CA, PIK3CD, and PIK3C2B) revealed amplification of PIK3C2B (1q32) in 6 tumors (6%). Overexpression of PIK3C2B mRNA was detected in 4 of these cases. PIK3CD (1p36.2) and PIK3CA (3q26.3) were not amplified but PIK3CD mRNA was overexpressed in 6 tumors (6%). Amplification and overexpression of AKT1 was detected in a single case of gliosarcoma. The IRS1, PIK3R1, PIK3R2, AKT2, AKT3, FRAP1, and RPS6KB1 genes were neither amplified nor overexpressed in any of the tumors. Taken together, our data indicate that different genes related to the Pi3k/Akt signalling pathway may be aberrant in glioblastomas.

L3 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:453249 CAPLUS
DOCUMENT NUMBER: 139:191809
TITLE: Transgenic mice with dominant negative PKC-theta in skeletal muscle: A new model of insulin resistance and obesity
AUTHOR(S): Serra, C.; Federici, M.; Buongiorno, A.; Senni, M. I.; Morelli, S.; Segratella, E.; Pascuccio, M.; Tiveron, C.; Mattei, E.; Tatangelo, L.; Lauro, R.; Molinaro, M.; Giaccari, A.; Bouche, Marina
CORPORATE SOURCE: Department of Histology and Medical Embryology, University of Rome "La Sapienza", Rome, Italy
SOURCE: Journal of Cellular Physiology (2003), 196(1), 89-97
CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Protein kinase C θ (PKC-θ) is the PKC isoform predominantly expressed in skeletal muscle, and it is supposed to mediate many signals necessary for muscle histogenesis and homeostasis, such as TGFβ, nerve-dependent signals and insulin. To study the role of PKC-θ in these mechanisms we generated transgenic mice expressing a "kinase dead" mutant form of PKC-θ (PKC-θK/R), working as "dominant neg.," specifically in skeletal muscle. These mice are viable and fertile, however, by the 6-7 mo of age, they gain weight, mainly due to visceral fat deposition. Before the onset of obesity (4 mo of age), they already show increased fasting and fed insulin levels and reduced insulin-sensitivity, as measured by ipITT, but normal glucose tolerance, as measured by ipGTT. After the 6-7 mo of age, transgenic mice develop hyperinsulinemia in the fasting and fed state. The ipGTT revealed in the transgenic mice both hyperglycemia and hyperinsulinemia. At the mol. level, impaired activation of the IR/IRS/PI3K pathway and a significant decrease both in the levels and in insulin-stimulated activation of the serine/threonine

kinase Akt were observed Taken together these data demonstrate that over-expression of dominant neg. PKC-θ in skeletal muscle causes obesity associated to insulin resistance, as demonstrated by defective receptor and post-preceptor activation of signaling cascade.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:129407 CAPLUS
DOCUMENT NUMBER: 134:261420
TITLE: Specific inhibition by hGRB10ζ of insulin-induced glycogen synthase activation: evidence for a novel signaling pathway
AUTHOR(S): Mounier, C.; Lavoie, L.; Dumas, V.; Mohammad-Ali, K.; Wu, J.; Nantel, A.; Bergeron, J. J. M.; Thomas, D. Y.; Posner, B. I.
CORPORATE SOURCE: The Polypeptide Hormone Laboratory, McGill University, Montreal, QC, H3A 2B2, Can.
SOURCE: Molecular and Cellular Endocrinology (2001), 173(1-2), 15-27
CODEN: MCEND6; ISSN: 0303-7207
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Grb10 is a member of a family of adapter proteins that binds to tyrosine-phosphorylated receptors including the insulin receptor kinase (IRK). In this study recombinant adenovirus was used to over-express hGrb10ζ, a new Grb10 isoform, in primary rat hepatocytes and the consequences for insulin signaling were evaluated. Over-expression of hGrb10ζ resulted in 50% inhibition of insulin-stimulated IRK autophosphorylation and activation. Anal. of downstream events showed that hGrb10ζ over-expression specifically inhibits insulin-stimulated glycogen synthase (GS) activity and glycogen synthesis without affecting insulin-induced IRS1/2 phosphorylation, PI3-kinase activation, insulin like growth factor binding protein-1 (IGFBP-1) mRNA expression, and ERK1/2 MAP kinase activity. The classical pathway from PI3-kinase through Akt-PKB/GSK-3 leading to GS activation by insulin was also not affected by hGrb10ζ over-expression. These results indicate that hGrb10ζ inhibits a novel and presently unidentified insulin signaling pathway leading to GS activation in liver.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 22 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:250874 BIOSIS
DOCUMENT NUMBER: PREV200100250874
TITLE: Serine residues 1177/78/82 of the insulin receptor are required for substrate phosphorylation but not autophosphorylation.
AUTHOR(S): Bossenmaier, Birgit; Strack, Volker; Stoyanov, Borislav; Kruetzfeldt, Jan; Beck, Alexander; Lehmann, Rainer; Kellerer, Monika; Klein, Harald; Ullrich, Axel; Lammers, Reiner; Haering, Hans-Ulrich [Reprint author]
CORPORATE SOURCE: Med. Klinik u. Poliklinik, Innere Med. IV, Eberhard-Karls-Universitaet Tuebingen, Otfried-Mueller-Str. 10, D-72076, Tuebingen, Germany
hans-ulrich.haering@med.uni-tuebingen.de
SOURCE: Diabetes, (June, 2000) Vol. 49, No. 6, pp. 889-895. print.
CODEN: DIAEAZ. ISSN: 0012-1797.
DOCUMENT TYPE: Article

LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002

AB Serine residues of the human insulin receptor (HIR) may be phosphorylated and negatively regulate the insulin signal. We studied the impact of 16 serine residues in HIR by mutation to alanine and co-over-expression in human embryonic kidney (HEK) 293 cells together with the docking proteins insulin receptor substrate (IRS)-1, IRS-2, or (SHC) Src homologous and collagen-like. As a control, IRS-1 was also cotransfected with an HIR with a juxtamembrane deletion (HIRDELTAJM) and therefore not containing the domain required for interaction with IRS-1. Coexpression of HIR with IRS-1, IRS-2, and SHC strongly enhanced tyrosine phosphorylation of these proteins. A similar increase in tyrosine phosphorylation was observed in cells overexpressing IRS-1, IRS-2, or SHC together with all HIR mutants except HIRDELTAJM and a mutant carrying exchanges of serines 1177, 1178, and 1182 to alanine (HIR1177/78/82), although this mutant showed normal autophosphorylation. Analysis of total cell lysates with anti-phosphotyrosine antibodies showed that in addition to the over-expressed substrates, other cellular proteins displayed reduced levels of tyrosine phosphorylation in these cells. To study consequences for phosphatidylinositol 3-kinase (PI 3-kinase) activation, we established stable NIH3T3 fibroblast cell lines overexpressing wild-type HIR, HIR1177/78/82, and other HIR mutants as the control. Again, HIR1177/78/82 showed normal autophosphorylation but showed a clear decrease in tyrosine phosphorylation of endogenous IRS-1 and activation of PI 3-kinase. This decrease in kinase activity also occurred in an in vitro kinase assay towards recombinant IRS-1. Finally, we performed a separation of the phosphopeptides by high-performance liquid chromatography and could not detect any differences in the profiles of HIR and HIR1177/78/82. In conclusion, we have defined a region in HIR that is important for substrate phosphorylation but not autophosphorylation. Therefore, this mutant may provide new insights into the mechanism of kinase activation and substrate phosphorylation.

L3 ANSWER 19 OF 22 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:336043 BIOSIS
DOCUMENT NUMBER: PREV200000336043
TITLE: The juxtamembrane but not the carboxyl-terminal domain of the insulin receptor mediates insulin's metabolic functions in primary adipocytes and cultured hepatoma cells.
AUTHOR(S): Paz, K.; Boura-Halfon, S.; Wyatt, L. S.; LeRoith, D.; Zick, Y. [Reprint author]
CORPORATE SOURCE: Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Journal of Molecular Endocrinology, (June, 2000) Vol. 24, No. 3, pp. 419-432. print.
CODEN: JMLEEI. ISSN: 0952-5041.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Aug 2000
Last Updated on STN: 7 Jan 2002

AB Insulin-stimulated signaling pathways are activated upon interactions between the intracellular domains of the receptor and its downstream effectors. Insulin receptor substrate proteins (IRS-1, -2, -3 and -4) are the best-studied substrates for the insulin receptor kinase (IRK). We have previously shown that IRS-1 and IRS-2 interact with the juxtamembrane (JM) but not with the carboxyl-terminal (CT) region of the insulin receptor (IR) in vitro. However, the precise role of these IR regions in mediating insulin's bioeffects is still unresolved. In the present work we made use of vaccinia virus as a vector for quantitative

expression of the JM and CT domains within the cytoplasm of physiologically insulin-responsive primary rat adipocytes and rat hepatoma Fao cells. We could demonstrate that overexpression of either the JM or the CT domains did not inhibit either insulin binding or insulin-stimulated receptor autophosphorylation. In contrast, metabolic effects such as insulin-induced glucose utilization in adipocytes, and insulin-induced amino acid utilization in Fao hepatoma cells were inhibited (70-80%) in cells over-expressing the JM but not the CT domains of IR. The inhibitory effects of the overexpressed JM domain were accompanied by inhibition of insulin-stimulated IRS-1 phosphorylation, decreased IRS-1-associated PI3K activity, and decreased phosphorylation of the downstream effectors of PI3K, PKB and p70 S6K. Insulin-stimulated thymidine incorporation in Fao cells was also inhibited (40%) upon overexpression of the JM but not the CT region of IR. Our findings suggest that interactions between the JM region of IR and its downstream effectors are obligatory for insulin-stimulated metabolic functions in physiologically relevant insulin responsive cells. They also rule out the possibility that interaction of proteins, including PI3K, with the CT domain can provide an alternative pathway.

L3 ANSWER 20 OF 22 EMBASE

ACCESSION NUMBER: 2000326752 EMBASE
TITLE: The functional significance of Shc in insulin signaling as a substrate of the insulin receptor.
AUTHOR: Sasaoka, T., Dr. (correspondence); Kobayashi, M.
CORPORATE SOURCE: Dept. of Clinical Pharmacology, Toyama Med. and Pharmaceut. Univ., 2630 Sugitani, Toyama 930-0194, Japan.
SOURCE: Endocrine Journal, (2000) Vol. 47, No. 4, pp. 373-381.
Refs: 37
ISSN: 0918-8959 CODEN: ENJOEO
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
003 Endocrinology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Oct 2000
Last Updated on STN: 5 Oct 2000

AB Shc is composed of 46-, 52-, 66-kDa isoforms which arise from alternative splicing of the primary Shc transcript. Upon insulin stimulation, the activated insulin receptor interacts with Shc. The NPXY motif around 960-Tyr residue of the insulin receptor binds to the N-terminal PTB domain of Shc. Subsequently, the 52-kDa, and, to a lesser extent, the 46-kDa Shc isoforms are tyrosine phosphorylated. Although Tyr-239/240 and Tyr-317 residues are the possible candidates of Shc phosphorylation sites, insulin predominantly phosphorylates the Shc Tyr-317 residue. Phosphorylated Shc binds to Grb2 which forms a complex with Sos guanine nucleotide exchange factor for p21ras. Both tyrosine-phosphorylated Shc and IRS can bind to Grb2, but Shc.ovrhdot.Grb2.ovrhdot.Sos is the predominant coupling pathway from the activated insulin receptor to p21ras. Along this line, microinjection of anti-Shc antibody inhibited insulin-induced mitogenesis, and the guanine nucleotide exchange activity for p21ras is tightly associated with Shc, but not with IRS. On the other hand, insulin only transiently activates p21ras for the strict hormonal regulation. For this regulation, longer time of insulin treatment deactivates p21ras by dissociation of Sos from the Shc.ovrhdot.Grb2.ovrhdot.Sos complex while Shc is still complexed with Grb2. Thus, Shc plays a critical role in insulin-induced mitogenesis through regulation of p21ras activity. As regards the impact of Shc on the metabolic aspects, Shc is shown to compete with IRS as the substrate of the insulin receptor. Thus, IRS mediated downstream signaling leading to glycogen synthesis was decreased

by over-expression of Shc. Taken together, Shc appears to play an important role in insulin induced mitogenesis, whereas Shc may not be required for regulation of the metabolic aspects of insulin.

L3 ANSWER 21 OF 22 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN DUPLICATE 7

ACCESSION NUMBER: 1999:442983 BIOSIS
DOCUMENT NUMBER: PREV199900442983
TITLE: The carboxyl terminal extension of the Drosophila insulin receptor homologue binds IRS-1 and influences cell survival.
AUTHOR(S): Marin-Hincapie, Mireya; Garofalo, Robert S. [Reprint author]
CORPORATE SOURCE: Pfizer Inc., Groton, CT, 06340-8002, USA
SOURCE: Journal of Biological Chemistry, (Aug. 27, 1999) Vol. 274, No. 35, pp. 24987-24994. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Oct 1999
Last Updated on STN: 26 Oct 1999

AB The Drosophila insulin receptor (INR) homolog includes an extension of approximately 400 amino acids at the carboxyl-terminal end of its beta subunit containing several tyrosine-based motifs known to mediate interactions with signaling proteins. In order to explore the role of this extension in INR function, mammalian expression vectors encoding either the complete INR beta subunit (beta-Myc) or the INR beta subunit without the carboxyl-terminal extension (betaDELTA) were constructed, and the membrane-bound beta subunits were expressed in 293 and Madin-Darby canine kidney cells in the absence of the ligand-binding alpha subunits. beta-Myc and betaDELTA proteins were constitutively active tyrosine kinases of 180 and 102 kDa, respectively. INR beta-Myc co-immunoprecipitated a phosphoprotein of 170 kDa identified as insulin receptor substrate-1 (IRS-1), whereas INR betaDELTA did not, suggesting that the site of interaction was within the carboxyl-terminal extension. IRS-1 was phosphorylated on tyrosine to a much greater extent in cells expressing INR beta-Myc than in parental or INR betaDELTA cells. Despite this, a variety of PTB or SH2 domain-containing signaling proteins, including IRS-2, mSos-1, Shc, p85 subunit of phosphatidylinositol 3-kinase, SHP-2, Raf-1, and JAK2, were not associated with the INR beta-MyccntdotIRS-1 complex. Over-expression of INR beta-Myc and betaDELTA kinases conferred an equivalent increase in cell proliferation in both 293 and Madin-Darby canine kidney cells, indicating that this growth response is independent of the carboxyl-terminal extension. However, INR beta-Myc-expressing cells exhibited enhanced survival relative to parental and betaDELTA cells, suggesting that the carboxyl-terminal extension, through its interaction with IRS-1, plays a role in the regulation of cell death.

L3 ANSWER 22 OF 22 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1997:751426 CAPLUS
DOCUMENT NUMBER: 128:57610
ORIGINAL REFERENCE NO.: 128:11142h,11143a
TITLE: Insulin receptor substrate -2 (IRS-2) can mediate the action of insulin to stimulate translocation of GLUT4 to the cell surface in rat adipose cells
AUTHOR(S): Zhou, Lixin; Chen, Hui; Lin, Chung H.; Cong, Li-Na; Mcgibbon, Margaret A.; Sciacchitano, Salvatore; Lesniak, Maxine A.; Quon, Michael J.; Taylor, Simeon I.

CORPORATE SOURCE: Diabetes Branch, NIDDK, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Journal of Biological Chemistry (1997), 272(47), 29829-29833
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Insulin receptor substrates-1 and -2 (IRS-1 and -2) are important substrates of the insulin receptor tyrosine kinase. Previous studies have focused upon the role of IRS-1 in mediating the actions of insulin. In the present study, we demonstrate that IRS-2 can mediate translocation of the insulin responsive glucose transporter GLUT4 in a physiol. relevant target cell for insulin action. Co-immunopptn. expts. performed on cell lysates derived from freshly isolated rat adipose cells incubated in the presence or absence of insulin indicated that twice as much phosphatidylinositol 3-kinase was associated with endogenous IRS-1 as with IRS-2 after insulin stimulation. When rat adipose cells in primary culture were transfected with expression vectors for IRS-1 or IRS-2, we observed 40-fold over-expression of human IRS-1 or murine IRS-2. In addition, anti-phosphotyrosine immunoblotting expts. confirmed that the recombinant substrates were phosphorylated in response to insulin stimulation. To examine the role of IRS-2 in insulin-stimulated translocation of GLUT4, we studied the effects of overexpression of IRS-1 and -2 on translocation of a co-transfected epitope-tagged GLUT4 (GLUT4-HA). Overexpression of IRS-1 or IRS -2 in adipose cells resulted in a significant increase in the basal level of cell surface GLUT4 (in the absence of insulin). Interestingly, at maximally effective concns. of insulin (60 nM), the level of cell surface GLUT4 in cells overexpressing IRS-1 or -2 significantly exceeded the maximal recruitment observed in the control cells (160 and 135% of control, resp.; $p < 0.003$). Our data directly demonstrate that IRS-2, like IRS-1, is capable of participating in insulin signal transduction pathways leading to the recruitment of GLUT4. Thus, IRS-2 may provide an alternative pathway for critical metabolic actions of insulin.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	78.99	79.21

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.28	-3.28

FILE 'STNGUIDE' ENTERED AT 13:36:04 ON 10 FEB 2009

FILE CONTAINS CURRENT INFORMATION.
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=> logout
LOGOUT IS NOT A RECOGNIZED COMMAND
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For a list of commands available to you in the current file, enter

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=> logoff
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FULL ESTIMATED COST	1.05	80.26

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-3.28

STN INTERNATIONAL LOGOFF AT 13:45:03 ON 10 FEB 2009